Governor's Marijuana Advisory Commission
Education and Prevention Subcommittee
(Executive Order No. 15-17)

November 13, 2017

Report on Existing Primary Research on Key Health and Safety Endpoints

(i) Injury and Death

According to a report by the National Academies of Science, Engineering and Medicine:

"There is no or insufficient evidence to support or refute a statistical association between cannabis use and**:**

- All-cause mortality (self-reported cannabis use)
- Occupational accidents or injuries (general, non-medical cannabis use)
- Death due to cannabis overdose"[1]

Bahorik et al. (2017) examined medical conditions present in patients enrolled in an integrated healthcare system in northern California with substance use disorders including cannabis use disorder (CUD) compared to demographically matched patients without CUD. They found significantly higher rates of diagnosable medical conditions in those patients with CUD compared to non-CUD patients [2] (see Table 1). In a longitudinal study. Reece et al. (2016) found that: "cannabis is an interactive cardiovascular risk factor (additional to tobacco and opioids), shows a prominent dose-response effect and is robust to adjustment. Cannabis is associated with an acceleration of the cardiovascular age, which is a powerful surrogate for the organismal-biological age" (p. 1)[3] In a review article, Franz & Frishman (2016) found a 4-fold increased risk of a myocardial infarction (MI – "heart attack") within 60 minutes after marijuana consumption as well as a 1-4% annual increased risk of an MI among daily marijuana users[4]. Rezkalla et al. (2016) conclude their review by stating "Despite…strong evidence for deleterious effects on the cardiovascular system, marijuana use remains common both for medical treatment and as a recreational substance. Evidence suggests that marijuana use can serve as a trigger for acute coronary syndromes and that marijuana-related vascular complications are associated with elevated mortality[5]" (p. 453). Draz et al. (2017)

[1] Committee on the Health Effects of Marijuana (2017). The Health Effects of Cannabis and Cannabinoids: The Current State of Evidence and Recommendations for Research. Washington, DC: National Academies Press.
[2] Bahorik et al. (2017). Alcohol, Cannabis, and Opioid Use Disorders and Disease Burden in an Integrated Health Care System. *Journal of Addiction Medicine, 11*, 3-9.
[3] Reece et al. (2016). Cannabis Exposure as an Interactive Cardiovascular Risk Factor and Accelerant of Organismal Ageing: A Longitudinal Study. *BMJ Open Nov 7;6(11):e011891. doi: 10.1136/bmjopen-2016-011891*.
[4] Franz, C.A. & Frishman, W.H. (2016). Marijuana Use and Cardiovascular Disease. *Cardiology in Review, 24*, 158-162.
[5] Rezkalla et al. (2016). Cardiovascular Effects of Marijuana. *Journal of Cardiovascular Pharmacology and Therapeutics, 21*, 452-455.

investigated male patients under 40 years of age with an acute MI. They concluded that "cannabis smoking could be a potential risk factor for the development of cardiac ischemia[6]" (p. 1).

[Weight-of-Evidence Category[7]] *Limited Evidence to support or refute a statistical association between cannabis use and all-cause mortality, occupational injuries, or deaths due to cannabis overdose*

Cannabinoid Hyperemesis Syndrome (CHS): First reported in 2004, CHS typically presents in the ED as cyclical episodes of vomiting, nausea, and stomach pain and is always predated by at least weekly marijuana use and reliably stops when marijuana use ceases. Pélisser et al. (2016) suggest that CHS is likely to be significantly underdiagnosed because ED staff do not typically delve into drug histories in patients with such an immediate problem. This can result in repeated hospitalizations and potential esophageal distress. Sorensen et al. (2016) provided a review of the literature on CHS; they suggest that "The pathophysiology underlying CHS is unclear. Cannabis cessation appears to be the best treatment" (p. 1) [8]

[Weight-of-Evidence Category] *Substantial Evidence for association between cannabis use and cannabinoid hyperemesis syndrome*

Emergency Department (ED) Use: Kim & Monte (2016) reported that "the prevalence of hospitalizations for marijuana exposure in patients aged 9 and older doubled after the legalization of medical marijuana and that ED visits nearly doubled after the legalization of recreational marijuana. In the years after both medical and recreational marijuana legalization, the call volume [to the Colorado poison control center] for marijuana exposure doubled compared with that during the year before legalization" (p. 2)[9].

[Weight-of-Evidence Category] *Substantial Evidence for association between cannabis use and increased Emergency Department use*

Fatal Car Crashes: The AAA Foundation for Traffic Safety (2016) examined fatal crash data from Washington state from 2010 to 2014 and concluded: "From 2010 through 2013, the estimated number and proportion of drivers involved in fatal crashes who had a detectable concentration of THC in their blood ranged from a low of 48 (7.9%) to a high of 53 (8.5%). The number and proportion both doubled from 49 (8.3%) in 2013 to 106 (17.0%) in 2014 [when recreational marijuana sales began][10]." Other reports also found a significant increase in marijuana-related traffic

[6] Draz et al. (2017). Marijuana Use in Acute Coronary Syndromes. The American Journal of Drug and Alcohol Abuse, 43, 576-582.
[7] See Appendix 2
[8] Pélissier et al. (2016). Cannabis Hyperemesis Syndrome in the Emergency Department: How can a Specialized Addiction Team be Useful? A Pilot Study. *Journal of Emergency Medicine, 51*, 544-551.
[9] Kim & Monte (2016). Colorado Cannabis Legalization and Its Effect on Emergency Care. *Annals of Emergency Medicine, 68*, 71-75.
[10] AAA Foundation for Public Safety (2016). Prevalence of Marijuana Involvement in Fatal Crashes: Washington 2010-2014. https://www.aaafoundation.org/prevalence-marijuana-use-among-drivers-fatal-crashes-washington-2010-2014

fatalities following legalization in Washington and Colorado[11],[12]. In Colorado, there were 55 fatalities in 2013 with marijuana confirmed in the driver's blood at levels above their legal limit. In 2016, this number rose to 125. Li et al. (2017) found marijuana use to be an independent risk factor in the initiation of fatal two-car crashes. "This study also confirms that use of marijuana alone increases crash culpability significantly, which is consistent with findings from previous meta-analyses, experimental, and case control studies[13]." (p. 345) In Vermont in 2016 there were 14 alcohol-related car crash fatalities while 18 fatalities were marijuana-related. In 2017 as of October 3, there were 5 alcohol-related and 10 marijuana-related car crash fatalities[14]. For comparison purposes we note that in 2016 there were 2 opioid-related car crash fatalities and to date in 2017 there has been 1.

[Weight-of-Evidence Category*] Moderate Evidence for association between cannabis use and fatal car crashes*

Vermont specific data are presented in Appendix 1.

(ii) Prenatal, perinatal exposure to marijuana

Prevalence: Brown et al. (2017) reported that "among pregnant women, the prevalence of past-month marijuana use increased 62% from 2002 to 2014. Prevalence was highest among women aged 18-25 years, indicating that young women are at greater risk for prenatal marijuana use" (p. 208)[15]. Volkow et al. (2017) commented in an accompanying editorial on a growing number of concerning internet posts promoting marijuana to treat pregnancy-related nausea; Volkow et al. stated "pregnant women and those considering becoming pregnant should be advised to avoid using marijuana or other cannabinoids either recreationally or to treat their nausea" (p.130)[16].

[Weight-of-Evidence Category] *Moderate Evidence for concerning increasing use among pregnant women.*

Long-Term Offspring Outcomes: Richardson et al. (2016) provided a theoretical review of the "Double Hit Hypothesis" of prenatal cannabis exposure (PCE)[17]. They argue that PCE not only adversely perturbs fetal neurodevelopment (the first "hit") which compromises the endogenous

[11] Rocky Mountain High Intensity Drug Trafficking Area (2017). The Legalization of Marijuana in Colorado: The Impact, Volume 5. http://www.rmhidta.org/html/FINAL%202017%20Legalization%20of%20Marijuana%20in%20Colorado%20The%20Impact%20Rich%20Text.pdf

[12] Washington State Traffic Commission (2016). Driver Toxicology Testing and the Involvement Marijuana in Fatal Crashes (2010-2014) – Revised. http://wtsc.wa.gov/wp-content/uploads/dlm_uploads/2015/10/Driver-Toxicology-Testing-and-the-Involvement-of-Marijuana-in-Fatal-Crashes_REVFeb2016.pdf

[13] Li et al. (2017). Role of Alcohol and Marijuana in the Initiation of Fatal Two-Car Crashes. Annals of Epidemiology, 27, 342-347.

[14] Agency of Transportation Motor Vehicle Crash Facts 2016 and 2017 Fatal/Fatality Data.

[15] Brown et al. (2017). Trends in Marijuana Use among Pregnant and Non-Pregnant Reproductive Aged Women 2002-2014. *Journal of the American Medical Association, 317*, 207-209.

[16] Volkow et al. (2017). The Risks of Marijuana Use during Pregnancy. *Journal of the American Medical Association, 317*, 129-130.

[17] Richardson et al. (2016). Prenatal Cannabis Exposure - the "first hit" to the Endocannabinoid System. *Neurotoxicology and Teratology, 58*, 5-14.

cannabinoid signaling system to allow for a specific phenotype that will be more vulnerable to postnatal stressor (the second "hit") thereby "predisposing the offspring to abnormalities in cognition and altered emotionality" (p. 1). McLemore & Richardson (2016) offer long-term data from three longitudinal studies to support the double hit hypothesis[18]. El Marroun et al. (2016) conducted an MRI study of 6 to 8-year-olds who were prenatally exposed to marijuana and/or tobacco compared to those who were not exposed. They concluded "overall, we detected significant associations between prenatal cannabis exposure and brain morphology in young children, particularly in the frontal brain" (p. 977[19]). Day et al. (2016) found that controlling for covariates such as other prenatal substance exposure, race, gender and offspring substance use at 22 years, prenatal marijuana exposure (PME) was significantly associated with offspring early age of onset of marijuana use compared to their non-PME peers. In addition, they reported an indirect effect of PME on the development of psychotic symptoms at age 22[20]. Sonan et al. (2015) reported that PME was linked to offspring marijuana use at age 22 controlling for significant covariates[21]. Prenatal alcohol exposure, race, and gender were also significant predictors of young adult use. Sonon et al. (2016) found two indirect pathways from PME to cannabis use disorder (CUD) at age 22. The first is from PME though depressive symptoms at age 10 and the second is from PME through early age of initiation of marijuana use[22]. Goldschmidt et al. (2016), reported significant indirect pathways from PME to "negative adult roles including increased risk of being arrested, lower educational attainment, having a child without being married, and unemployment" (p. 1). The pathways identified were PME → early age of marijuana initiation → negative adult roles, and PME → behavior problems at age 3 → early age of marijuana initiation → negative adult roles. Smith et al. (2016) reported data from another prospective longitudinal study – Ottawa Prenatal Prospective Study (OPPS). Functional MRI (fMRI) scans were performed on 16 offspring prenatally exposed to marijuana and 15 offspring who were not prenatally exposed to marijuana (mean age = 21) to assess four executive functioning tasks. "Capitalizing on the ability of fMRI to act as a window into the working brain and the wealth of information obtained from these young adults throughout their lives, the results endorse the findings that there are in fact long term neurophysiological consequences of prenatal marijuana exposure" (p. 4)[23].

The American College of Obstetricians and Gynecologists recently (October 2017) issued the following opinion about marijuana use during pregnancy: "Because of concerns regarding impaired neurodevelopment, as well as maternal and fetal exposure to the adverse effects of smoking, women who are pregnant or contemplating pregnancy should be encouraged to discontinue marijuana use. Obstetrician–gynecologists should be discouraged from prescribing

[18] McLemore & Richardson (2016). Data from Three Prospective Longitudinal Human Cohorts of Pre-Natal Marijuana Exposure and Offspring Outcomes from the Fetal Period Through Adulthood. *Data Brief, 9*, 753-757.
[19] El Marroun et al. (2016). Prenatal Cannabis and Tobacco Exposure in Relation to Brain Morphology: A Prospective Neuroimaging Study in Young Children. *Biological Psychiatry, 79*, 971-979.
[20] Day et al. (2015). Prenatal Marijuana Exposure, Age of Marijuana Initiation, and the Development of Psychotic Symptoms in Young Adults. *Psychological Medicine, 45*, 1779-1787.
[21] Sonon et al. (2015). Prenatal Marijuana Exposure Predicts Marijuana Use in Young Adulthood. *Neurotoxicology and Teratology, 47,* 10-15.
[22] Sonon et al. (2016). Developmental Pathways from Prenatal Marijuana Exposure to Cannabis Use Disorder in Young Adulthood. *Neurotoxicology and Teratology, 48,* 46-52.
[23] Smith et al. (2016). Prenatal Marijuana Exposure Impacts Executive Functioning into Young Adulthood: A fMRI Study. *Neurotoxicology and Teratology, 48,* 53-59.

or suggesting the use of marijuana for medicinal purposes during preconception, pregnancy, and lactation. Pregnant women or women contemplating pregnancy should be encouraged to discontinue use of marijuana for medicinal purposes in favor of an alternative therapy for which there are better pregnancy-specific safety data.[24]"

[Weight-of-Evidence Category] *Insufficient Evidence for association between maternal cannabis smoking and long-term offspring outcomes (cognitive function, subsequent substance use).*

(III) Psychosocial:

There is strong evidence that early and continuous use of marijuana has long term negative effects on psychosocial outcomes. Several longitudinal prospective studies have converged on the same results for using marijuana prior to age 18 (Arria et al., 2013[25]; Danielson et al., 2015[26]; Ferguson et al, 2015[27]; Meier et al., 2012[28]; Silins et al, 2014[29]).
These studies all found significantly increased risk of:

- not completing high school
- not enrolling or completing college
- low educational achievement level
- lower income
- unemployment and welfare dependence as an adult
- premature work force retirement due to disability
- reduction in IQ in middle adulthood

Silins et al. (2014) has demonstrated a strong linear, dose-dependent association between several of these adult outcomes and adolescent marijuana use – the heavier the use in terms of frequency, the worse the outcome. Furthermore, significant risks attach to frequencies as low as monthly use. The Silins et al. (2014) study is notable for its lengthy follow-up period of 25 years, and the large number of subjects available for analysis (more than 2,500 cases). It is also important to note that THC content of marijuana was less than 5% when these studies began measuring use when the participants were adolescents. Smart et al. (2017) recently analyzed 30,000,000 marijuana purchases in Washington State and found that THC potency averaged 20.6% for flowers and 68.7% for extracts[30]. In addition, 80% of past month use of marijuana is by daily or near daily users (Caulkins, 2017)[31].

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[24] ACOG Committee Opinion Number 722 (2017). Marijuana Use During Pregnancy and Lactation.
[25] Arria et al. (2013). Drug Use Patterns and Continuous Enrollment in college: Results from a Longitudinal Study. *Journal of Studies on Alcohol and Drugs, 74*, 71-83.
[26] Danielson et al. (2015). Cannabis Use among Swedish Med in Adolescence and the Risk of Adverse Life Outcomes: Results from a 20-Year Follow-Up Study. *Addiction, 110*, 1795-1802.
[27] Fergusson et al. (2015). Psychosocial Sequelae of Cannabis Use and Implications for Policy: Findings from the Christchurch Health and Development Study. *Social Psychiatry and Psychiatric Epidemiology, 50*, 1317-1326.
[28] Meier et al. (2012). Persistent Cannabis Users show Neuropsychological Decline from Childhood to Midlife. *Proceedings of the National Academy of Science, 109*, E2657-E2664.
[29] Silins et al. (2014). Young Adult Sequelae of Adolescent Cannabis Use: An Integrative Analysis. *Lancet Psychiatry, 1,* 286-293.
[30] Smart et al. (2017). Variation in Cannabis Potency and Prices in a Newly Legal Market: Evidence from 30 Million Cannabis Sales in Washington State. *Addiction*, published online July 4, 2017.
[31] Caulkins (August 2017). Real Options for Legalization. Keynote address presented at the National Cannabis Summit Denver, CO. https://ncc.expoplanner.com/files/18/SessionFilesHandouts/MGS2_Caulkins_1.pdf

The combination of early initiation (i.e., adolescence), more frequent use, and higher potency may have profound adverse implications for public health in the long-term. There is very little research on the relationship between frequency and potency of marijuana use. It could be that higher potency marijuana may reduce frequency of use, but this is currently an open question. To be clear, the time lags required to investigate these relationships are substantial. While nearly all the currently available longitudinal research suggests negative outcomes for early and persistent marijuana use (e.g., Fergusson et al., 2015; Meier et al., 2012; Silins et al., 2014) the overall impact on the general population will not be known for perhaps decades if marijuana use becomes widespread.[32]

[Weight-of-Evidence Category] *Moderate Evidence for cannabis use and impaired academic achievement, lower income and unemployment*

(iv) <u>Mental Health</u>

Early adolescent marijuana use has been linked to the development of anxiety disorders later in life. Degenhardt et al. (2012) found that among adolescents, regular marijuana use or a diagnosis of marijuana dependence was significantly associated with increased risk of anxiety disorders in adolescence and late young adulthood (age 29), even if individuals had stopped using marijuana[33].

Psychosis: There is evidence showing an increased risk of developing short-term, transient acute psychotic symptoms and, in some cases, chronic psychotic illness such as schizophrenia among early (adolescent) and persistent users of marijuana. There appears to be consensus regarding the finding that individuals at risk to develop schizophrenia through genetic factors (i.e. family history, high-risk genotype) and environmental factors (i.e. early onset child maltreatment/abuse) significantly increase that risk by using marijuana starting in adolescence (Radhakrishnan et al. 2014)[34].

Furthermore, it appears that early marijuana use accelerates the progression from symptoms to diagnosis such that at-risk marijuana users are diagnosed with schizophrenia several years earlier than at-risk nonusers (Myles et al., 2012; Large et al., 2011). However, there is some disagreement as to whether heavy marijuana use may facilitate or accelerate psychotic symptoms and diagnoses in individuals without an identified risk profile (Crean et al., 2011). Schizophrenia is a rare disorder, whether marijuana is an exacerbating risk factor or not.

This is an area where high potency marijuana may have a significant adverse effect because typically higher levels of the THC are associated with lower levels of cannabidiol (CBD) which may have antipsychotic (protective) effects. High potency THC has been associated with a significantly higher risk of first episode psychosis[35]. Volkow et al. (2016) reviewed the literature on the effects of marijuana use across several aspects of human behavior including psychosis and reported "…there is

[32] Chen & Searles (2017). Health Considerations in Regulating Marijuana in Vermont. *Preventive Medicine*, Published online June 8.

[33] Degenhardt et al. (2012). The Persistence of the Association between Adolescent Cannabis Use and Common Mental Disorders into Young Adulthood. *Addiction, 108,* 124-133.

[34] Radhakrishnan et al. (2014). Gone to Pot: A review of the Association between Cannabis and Psychosis. *Frontiers in Psychiatry*, published online May 22.

[35] DiForti et al. (2015). Proportion of Patients in South London with First-Episode Psychosis Attributable to Use of High Potency Cannabis: A Case Control Study. *Lancet Psychiatry, 2*, 233-238.

strong physiological and epidemiological evidence supporting a mechanistic link between cannabis use and schizophrenia. Tetrahydrocannabinol (particularly at high doses) can cause acute, transient, dose-dependent psychosis (schizophrenia-like positive and negative symptoms). In addition, prospective, longitudinal, epidemiological studies consistently report an association between cannabis use and schizophrenia is which cannabis use precedes psychosis independent of alcohol consumption and even after removing or controlling for those individuals who had used other drugs" (p. 294)[36]. Marconi et al. (2016) published a formal meta-analysis investigating the association between levels of cannabis use and risk of psychosis. Figure 1 is a graphical representation of their results. "OR" represents the odds ratio. This graph demonstrates a very strong linear relationship between marijuana exposure and the risk of developing a psychosis. The "exposure" measure is a calculated metric based on the data available from each study accounting for both frequency and length of use. "Current evidence shows that high levels of cannabis use increase the risk of psychotic outcomes and confirms a dose-response relationship between the level of use and the risk for psychosis" (p. 1262)[37]. These authors also recognize that potency may significantly affect their results: "we could only measure the degree of exposure without taking into account the potency of cannabis or the period of use. There is previous evidence that use of high-potency cannabis as well as early onset of use are stronger risk factors for psychoses" (p. 1267). Since 2015, there have been an additional 16 research studies published that directly support the link between early marijuana use and the development of psychosis.

[Weight-of-Evidence Category] Substantial Evidence for cannabis use and development of acute psychosis and chronic psychotic illness such as schizophrenia

PTSD: Johnson et al. (2016) reported on a study investigating the role of marijuana use and frequency of use in patients with PTSD. In a matched case-control design (marijuana users versus non-users), they found that marijuana use did not reduce PTSD symptoms. In addition, they found that "there was also no association between PTSD scores and frequency of cannabis use" (p. 439)[38]. Gentes et al. (2016) investigated marijuana use in a sample of veterans who presented at a specialty outpatient PTSD clinic. After controlling for several potential confounding influences (age, race, service area, and combat exposure) they reported that marijuana use was associated with significantly greater PTSD symptom severity, other drug use, hazardous alcohol use, depressive symptoms, and suicidality[39].

[Weight-of-Evidence Category] *Insufficient Evidence for cannabis use and development of PTSD or bipolar disorder*

(v) Problem Marijuana Use

Silins (2014) found a dose dependent relationship between frequency of use and risk of cannabis dependence as well as frequency of use and risk of other substance use and suicide attempts (see

[36] Volkow et al. (2016). Effects of Cannabis Use on Human Behavior Including Cognition, Motivation, and Psychosis: A Review. *JAMA Psychiatry, 73*, 292-297.
[37] Marconi et al. (2016). Meta-Analysis of the Association between Level of Cannabis Use and Risk of Psychosis. *Schizophrenia Bulletin, 42*, 1262-1269.
[38] Johnson et al. (2016). Mental Health Symptom Severity in Cannabis Using and Non-Using Veterans with Probable PTSD. *Journal of Affective Disorders, 190*, 439-442.
[39] Gentes et al. (2016). Prevalence and Correlates of Cannabis Use in an Outpatient VA Posttraumatic Stress Disorder Clinic. *Psychology of Addictive Behaviors, 30*, 415-421.

Figure 2). Hassin et al. (2015) reported a significant increase in CUD from 2001/02 to 2012/13. They found that the rate of CUD more than doubled over that time period (4.1%; 9.5%) among the general population. Among past year users of marijuana 30% manifested a CUD[40]. Hasin et al. (2016) found that CUD was significantly higher among those 18-29 and those with an annual income of less than $20,000. Those with a past year CUD were significantly more likely to also be diagnosed with alcohol and other drug use disorders, mood disorder (major depression, bipolar disorder), anxiety disorders, and posttraumatic stress disorder[41].

[Weight-of-Evidence Category] *Substantial Evidence for cannabis use frequency and development of cannabis use disorder, which is then subsequently associated with diagnosis of other psychiatric disorders*

(vi) Marijuana Use and Abuse of Other Substances

As stated above, past year CUD diagnosis is associated with other alcohol and drug use disorders (Hasin et al., 2016). Weinberger et al. (2016) investigated the association between marijuana use at baseline (Time 1) among individuals with no history of alcohol use disorder (AUD) and AUD three years later (Time 2). They found a five-fold increase in the incidence of AUD at Time 2 among marijuana users with no AUD at time 1 compared to nonusers of marijuana. They also found that individuals who did have an AUD at Time 1 and used marijuana had an increased use of a persistent AUD at Time 2 compared to individuals who had an AUD at time 1 but did not use marijuana[42]. Arteberry et al. (2016) studied the initiation, reinitiation, and persistence of non-medical prescription drug use (NMPDU) among non-users, prior users, and current users of opioids, tranquilizers and the association with marijuana, alcohol, and tobacco use. They report "notably, cannabis use was a consistent risk factor more than any other substance that increased the likelihood of NMPDU initiation as well as higher risk stages such as reinitiation and persistence, where cannabis (early onset and frequency) was the only substance that increased the likelihood of sedative/tranquilizer persistence. These findings suggest that cannabis use may play a role in the progression of opioid and sedative/tranquilizer use" (p. 91).[43]

Olfson et al. (2017) reported prospective data in a large sample showing that any past year cannabis use was associated with higher risk of both prevalence and incidence of nonmedical use of opioids three years later[44]. This article discusses previous research that appeared to demonstrate a relationship between medical marijuana availability and reduction in overdose death rates from prescription opioid

[40] Hasin et al. (2015). Prevalence of Marijuana Use Disorders in the United states Between 2001-2002 and 2012-2013. *JAMA Psychiatry, 72,* 1235-1242.
[41] Hasin et al. (2016). Prevalence and Correlates of DSM-5 Cannabis Use Disorder, 2012-2013: Findings from the National Epidemiological Survey on Alcohol and Related Conditions-III. American Journal of Psychiatry, 163, 588-599.
[42] Weinberger et al. (2016). Is Cannabis Use Associated with an Increased Risk of Onset and Persistence of Alcohol Use Disorders? A Three Year Prospective Study among Adults in the United States. *Drug and Alcohol Dependence, 161*, 363-367.
[43] Arteberry et al. (2016). The Effects of Alcohol, Cannabis, and Cigarette Use on the Initiation, Reinitiation, and Persistence of Non-Medical Use of Opioids, Sedatives, and Tranquilizers in Adults. *Drug and Alcohol Dependence, 159,* 86-92.
[44] Olfson et al. (2017). Cannabis Use and Risk of Prescription Opioid Use Disorder in the United States. *American Journal of Psychiatry*, epub ahead of print, September 26.

analgesics[45]. These three articles have been prominent in the push toward legalization. However, these authors (and others) point out that it is not possible to determine individual level of risk from these types of studies[46]. The report describes analyses of Wave 1 and Wave 2 (three years apart) data from the National Epidemiolocal Survey of Alcohol and Related Disorders (NESARC)[47].

Results (Background): Wave 1 individuals who reported any past-year cannabis use were more likely to be younger, male, have a past-year opioid use disorder, cannabis use disorder, other substance use disorder or any past year mood or anxiety order.

Results (Prospective Associations): "After adjustment for the background demographic and clinical characteristics[48], a strong association persisted between wave 1 cannabis use and wave 2 prevalent nonmedical opioid use. Among individuals without nonmedical opioid use during the 12 months before the wave 1 interview, ***there was a significant association between cannabis use at wave 1 and incident nonmedical opioid use during the follow-up period***." (p.3) Further "cannabis use at wave 1 was associated with a significant increase on the odds of prevalent and incident [initiators] prescription opioid use disorder during the follow-up period." (p.3) Thus, any cannabis use at wave 1 was significantly associated with an increase in prevalence of nonmedical opioid use as well as a significant increase in the number of new cases of nonmedical opioid use in wave two. This effect was dose dependent

"In a nationally representative sample of adults evaluated at waves 3 years apart, cannabis use was strongly associated with subsequent onset of nonmedical prescription opioid use and opioid use disorder. These results remained robust after controlling for the potentially confounding effects of several demographic and clinical covariates that were strongly associated with cannabis use. The association of cannabis use with the development of nonmedical opioid use was evident among adults without cannabis use disorders and among adults with moderate or more severe pain. Among adults with nonmedical prescription opioid use, cannabis use was associated with an increase in the level of nonmedical prescription opioid use at follow-up." (pp 3-4)

"Ecological studies reporting fewer opioid-related deaths and decreased opioid prescribing following passage of medical marijuana laws [Bradford & Bradford, 2016] have been interpreted in the media[49] and scientific literature[50] as supporting cannabis as a means of reducing opioid use disorder. Yet drawing inferences about the behavior of individuals from aggregated data can be misleading. It is possible, for example, that passage of medical marijuana laws increased local clinical awareness of opioid misuse, leading to earlier detection of high-risk patients or more cautious opioid prescribing practices. At the

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[45] Bachhuber et al.(2014). Medical Cannabis Laws and Opioid Analgesic Overdose Mortality in the United States. *JAMA Internal Medicine, 174*, 1668-1673.
Powell et al. (2015). Do medical marijuana laws reduce addictions and deaths related to pain killers? NBER Working Paper No. 21345. Cambridge, MA: National Bureau of Economic Research.
Bradford & Bradford (2016). Medical Marijuana Laws Reduce Prescription Medication Use in Medicare Part D. *Health Affairs, 35*, 1230-1236.

[46] Finney et al. (2015). What Ecological analyses Cannot Tell Us About Medical Marijuana Legalization and Opioid Pain Medication Mortality. *JAMA Internal Medicine, 175*, 655-656.

[47] NESARC "is a nationally representative sample of the noninstitutionalized adult U.S. population conducted by the U.S. Census Bureau under the direction of the National Institute on Alcoholism and Alcohol Abuse." (p.2)

[48] Adjusted for age, sex, race/ethnicity, other substance use disorders, any mood or anxiety disorder, and family history of drug use disorder, alcohol use disorder, depression, and antisocial/personality disorder at wave 1.

[49] Zhang (2016). Patients Are Ditching Opioid Pills for Weed: Can Marijuana Help Solve the Opioid Epidemic. Atlantic, February 2.

[50] Miller, (2016). Could Pot Help Solve the US Opioid Epidemic? *Science*, November 3.

individual level, cannabis use appears to substantially increase the risk of nonmedical opioid use. Moreover, the general association between cannabis use and subsequent use of illicit drugs is not explained by the legal status of cannabis. An association of early cannabis use with increased subsequent risk of other drug abuse has been reported in prospective co-twin studies in Australia, which has restrictive cannabis laws, and in the Netherlands, where cannabis is readily available." (pp 5-6)

"If cannabis use tends to increase opioid use, it is possible that the recent increase in cannabis use[51] may have worsened the opioid crisis." (p5)

Finally, we note that these associations occurred over 10 years ago when marijuana potency was significantly less than today (Smart et al., 2017; ElSohly et al., 2016[52]).

Another recent article suggests that legalization of marijuana in Colorado was associated in a reduction in the increase in opioid overdose deaths (Livingston et al., 2017[53]. They conclude their report by stating: "Although we found an apparent public health benefit in a reduction in opioid-related deaths following recreational cannabis legalization in Colorado, we note that expanded legalized cannabis use is also associated with significant potential harms. For policymakers to balance the potential beneficial and deleterious effects of these laws, researchers must continue to examine the full range of health effects in both clinic and population-level research."[54]

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[51] Hasin et al. (2015). Prevalence of Marijuana Use Disorders in the United States between 2001-2002 and 2012-2013. *JAMA Psychiatry, 72*, 1235-1242.

[52] ElSohly et al. (2016). Changes in Cannabis Potency Over the Past Two Decades (1995-2014): Analysis of Current Data in the United States. *Biological Psychiatry, 79*, 613-619.

[53] Livingston et al. (2017). Recreational Cannabis Legalization and Opioid-Related Deaths in Colorado, 2010-2015. *American Journal of Public Health, 107*, 1827-1829.

[54] In an attempt to reconcile the disparate results of these two studies (Olfson et al., 2017; Livingston et al., 2017) the lead authors of both studies were contacted. From Olfson: "My general thoughts on this and other ecological studies (see work by JH Kim et al., AJPH 2016; MA Bachhuber et al JAMA Psychiatry 2016; Shi Y et al Drug Alc Depend 2017) is that they are thought provoking, but because they offer no information on whether individuals who use cannabis either medically or recreationally have a lower or higher risk of developing adverse opioid-related events (death, motor vehicle accidents, etc.), they are of limited inferential validity. For the Livingston article, time periods before and after passage of the recreational cannabis use legislation in Colorado may differ in important ways, such as PDMP policy the authors' discuss, that influence the risks of opioid-related mortality. For example, how did the availability of naloxone rescue change over time in the state? How did clinical assessments of pain and opioid prescribing practices change during this period? Did access to MAT change over time? etc.

The basic problem here is that inferences about the nature of individuals cannot be directly deduced from inferences about the group to which the individual belongs - this is the ecological fallacy. In the US, for example, states with proportionately more immigrants have proportionately more households with incomes above $100,000/year, yet immigrants are significantly less likely than non-immigrants to have have household incomes above $100,000/year. As a result, it is not uncommon for ecological and clinical studies to yield results that appear to be odds with one another. As an example from my own work, years ago I did a study demonstrating that states with increased prescriptions of antidepressants to young people tended to have decreased youth suicide rates over the same time period. However, when I did a case/control study with individual depressed young people, I found that antidepressant use was in fact associated with an increased risk of suicide. "

From Livingston: "I'm not sure that I see their results as incompatible with ours, though I would say that it highlights the need for continued monitoring as these policies roll out. Couple quick thoughts:

While this report shows a statistical association (p =.043) between marijuana legalization and a modification of the rate of increase in opioid-related overdose deaths, other factors related to the opioid epidemic itself and unrelated to marijuana legalization may have played a part in these findings. For example, from 2013 to 2015 there was a 13% increase in use of naloxone by emergency medical services in Colorado[55]. Arrests for heroin possession increased 113% from 2013 to 2015[56]. Seizures of heroin increased 112% over that time frame[57]. From 2013 to 2015 there was a 53% increase in heroin treatment admissions[58]. These factors singly or in combination could account, at least in part, for any amelioration of the opioid overdose death rate independent of any considerations associated with marijuana legalization.

[Weight-of-Evidence Category] *Moderate Evidence for association between cannabis use and development of alcohol use disorder*
Limited Evidence for association between cannabis use and development of opioid use disorder

(vii) <u>Crime Rates</u>

N/A

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1. The NESARC sample is national and older than recreational cannabis policy changes. So for all of those surveyed, recreational cannabis would still be illegal at both the state and federal levels. It's possible cannabis use norms are different now in places where it is legal at the state level, which could lead to different usage patterns of other substances.
2. Their follow-up window is longer than ours (3 years our 2 years), so it's possible that the short term decreases in opioid related deaths we observed may reverse over time.
3. We are ultimately comparing different, but related, outcomes. It's possible that access to recreational cannabis could lead to increased opioid use without leading to increased opioid related deaths. Though I'm not sure what that mechanism and usage pattern would look like for that possibility.

Ultimately, I think we all have a lot more work to do before we fully understand the full impact of these laws. In addition to increased follow-ups and replications of our results in other states, I think replicating the analysis of the paper you sent in states with recreational cannabis would go a long way towards figuring this out."

[55] Colorado Department of Public Health and Environment (CDPHE) / Emergency Medical and Trauma Services' Data Section – Naloxone Summary 2011 – 2015
[56] Colorado Bureau of Investigation, Heroin Arrests in Colorado 2011 - 2015
[57] El Paso Intelligence Center (EPIC), National Seizure System (NSS) data
[58] Colorado department of Human services, Office of Behavioral Health

Table 1

Medical Conditions Among Patients with Cannabis Use Disorder Compared to Patients without CUD

Variable	Cannabis Use Disorders	
	SUD	Non-SUD
	n = 6787	n = 6787
Condition, %		
Any medical condition	41.9	23.0**
Acid-peptic disorders	11.9	5.2**
Arthritis	7.8	5.3**
Asthma	14.6	0.7**
Chronic kidney disease	1.0	0.4**
COPD	5.4	1.8**
Chronic pain	11.1	2.0**
Congestive heart failure	0.8	0.1**
Coronary atherosclerosis	1.6	0.5**
Diabetes mellitus	3.3	2.1**
End-stage renal disease	0.2	0.0**
Headaches	5.1	2.3**
Hepatitis C	2.6	0.3**
Hypertension	17.8	10.5**
Injury, poisoning/overdose	34.6	22.3**
Ischemic heart disease	3.0	1.1**
Pneumonia	2.5	0.8**
Obesity	6.6	3.7**
Osteoporosis	0.1	0.0
Stroke	0.5	0.1**

**p<.001

Figure 1

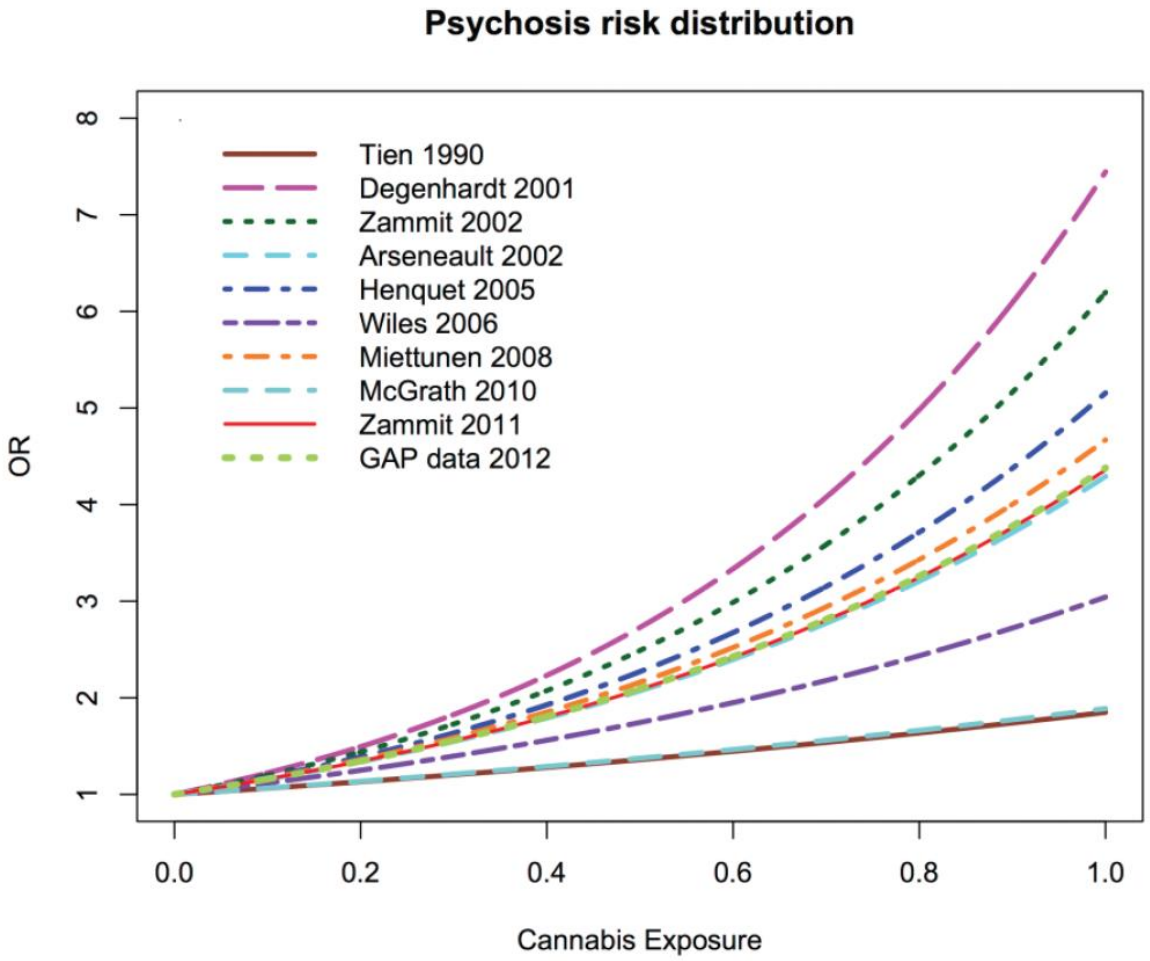
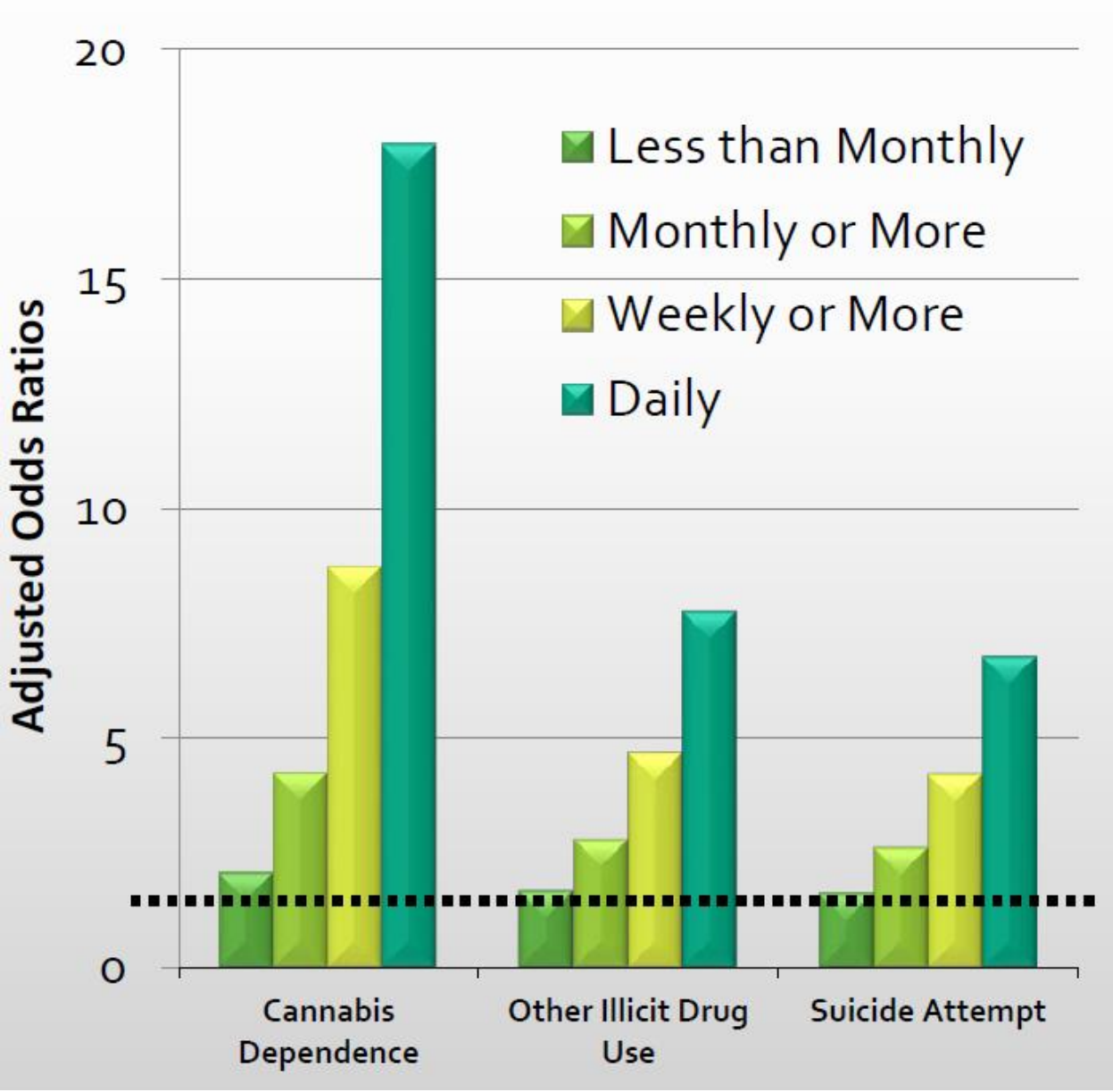


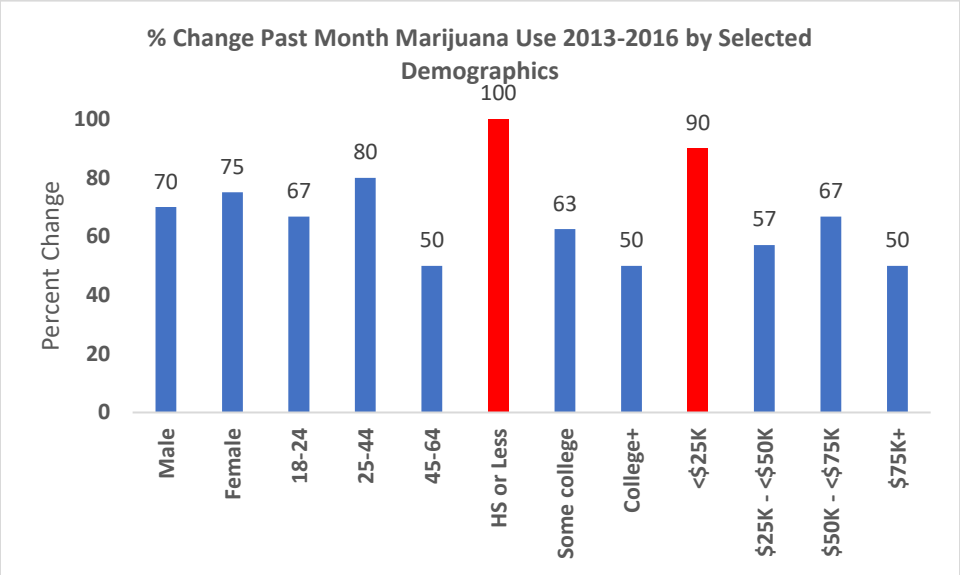
Figure 2

Frequency of Use and Risk of Cannabis Dependence, Other Drug Use, and Suicide Attempts



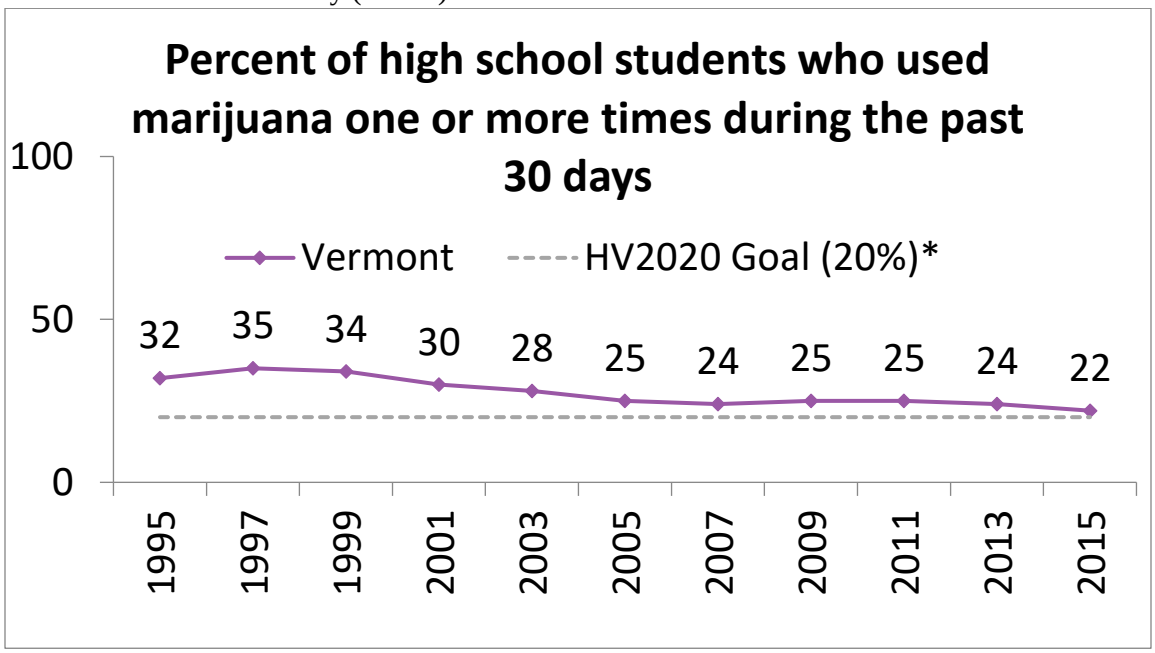
Appendix 1
Injury and Death: Vermont Specific Data

Prevalence of Use:
Behavioral Risk Factor Survey System (BRFSS)

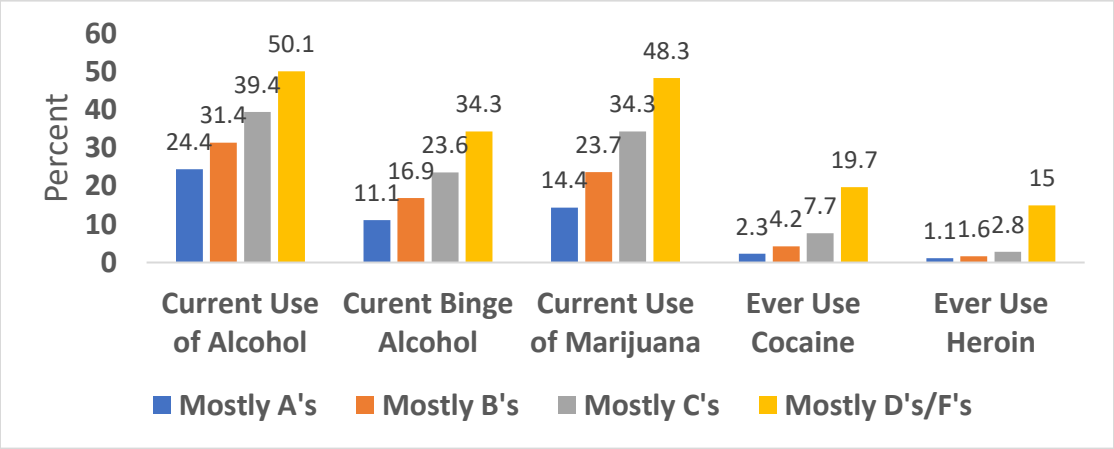


Note that the largest increase occurs among low educational attainment and those in the lowest income bracket.

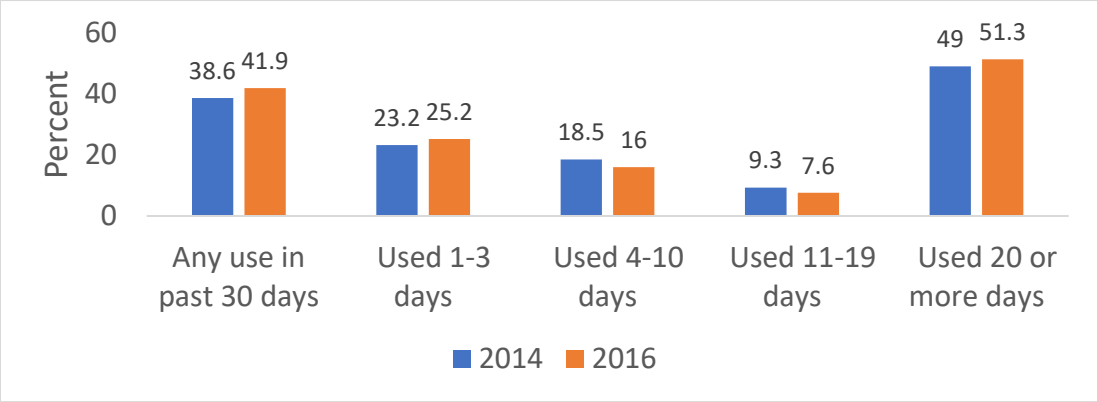
Youth Risk Behavior Survey (YRBS)



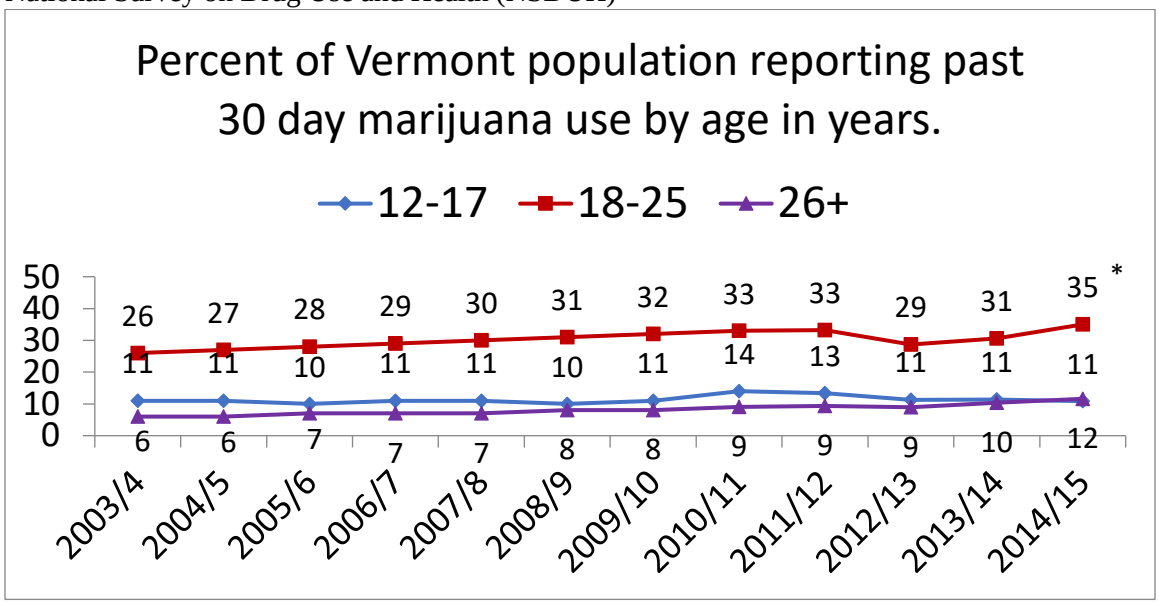
Vermont Youth Risk Behavior Survey – 2015: Prevalence by Self-Reported Grades (Adjusted)



Young Adult Survey (YAS)

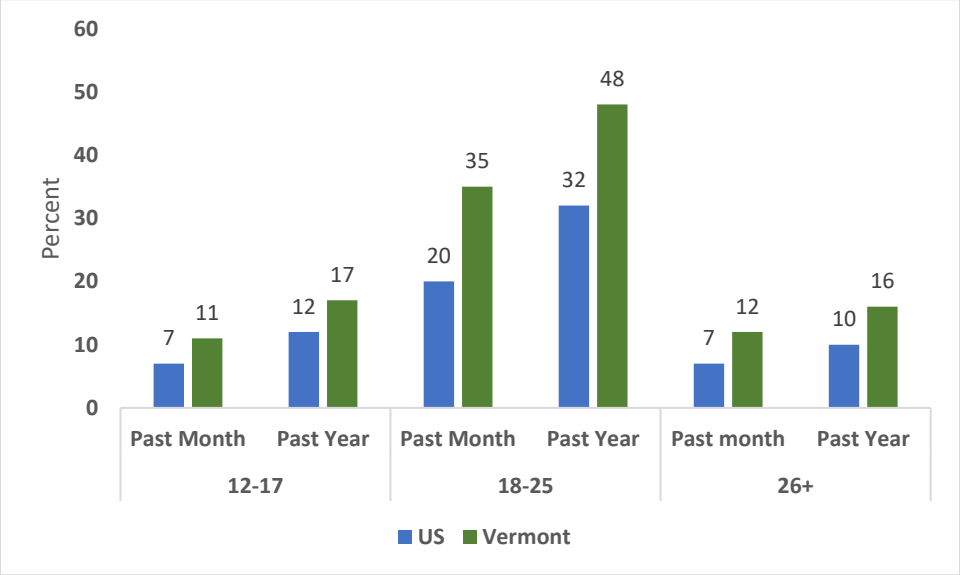


National Survey on Drug Use and Health (NSDUH)



*Significant Increase from 2013/14

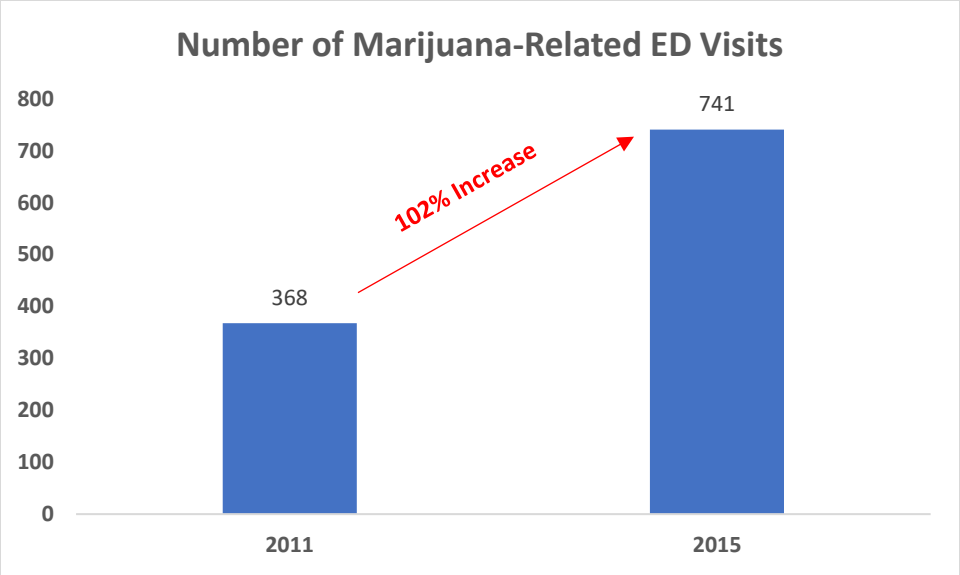
Past Month and Past Year Marijuana Use in the US and Vermont (2014/15)*



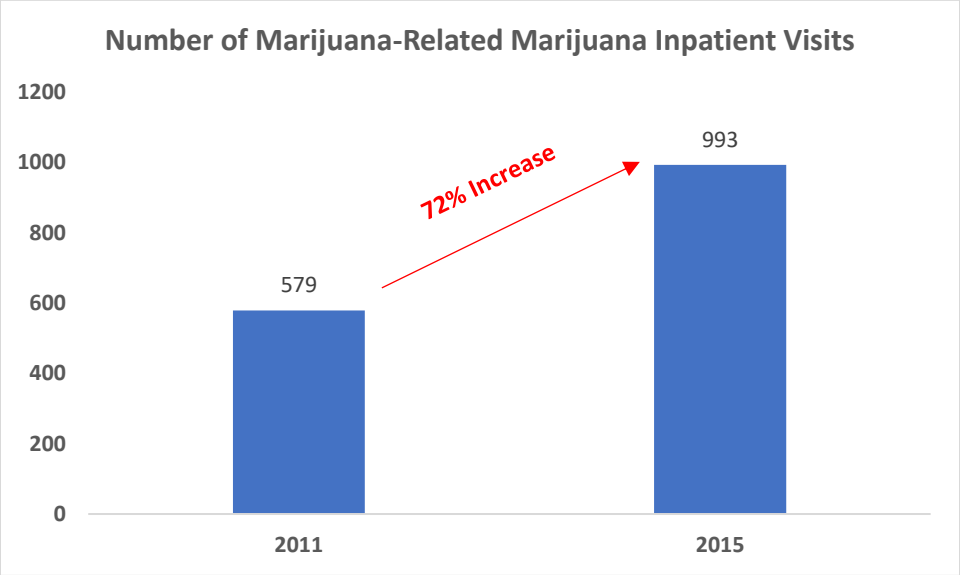
*All differences between US and Vermont are statistically significant for all age groups

Health

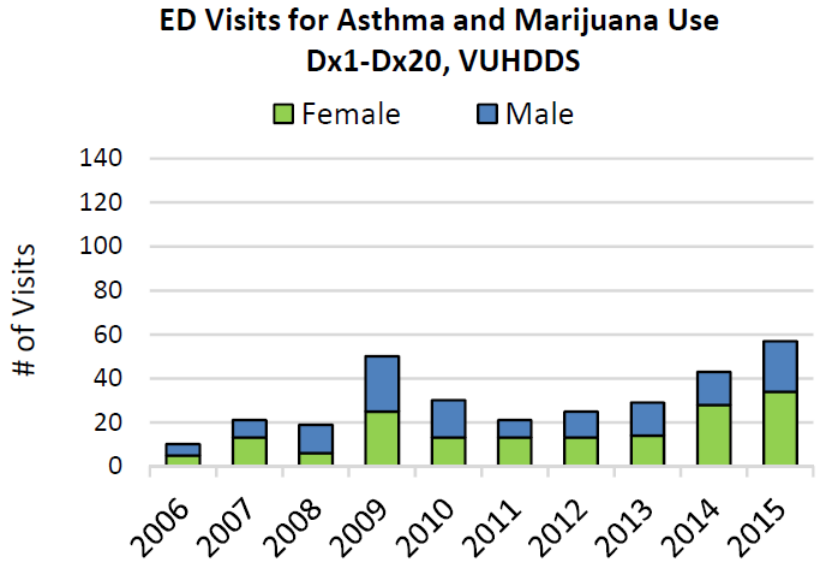
Vermont marijuana-related Emergency Department (ED) visits over time



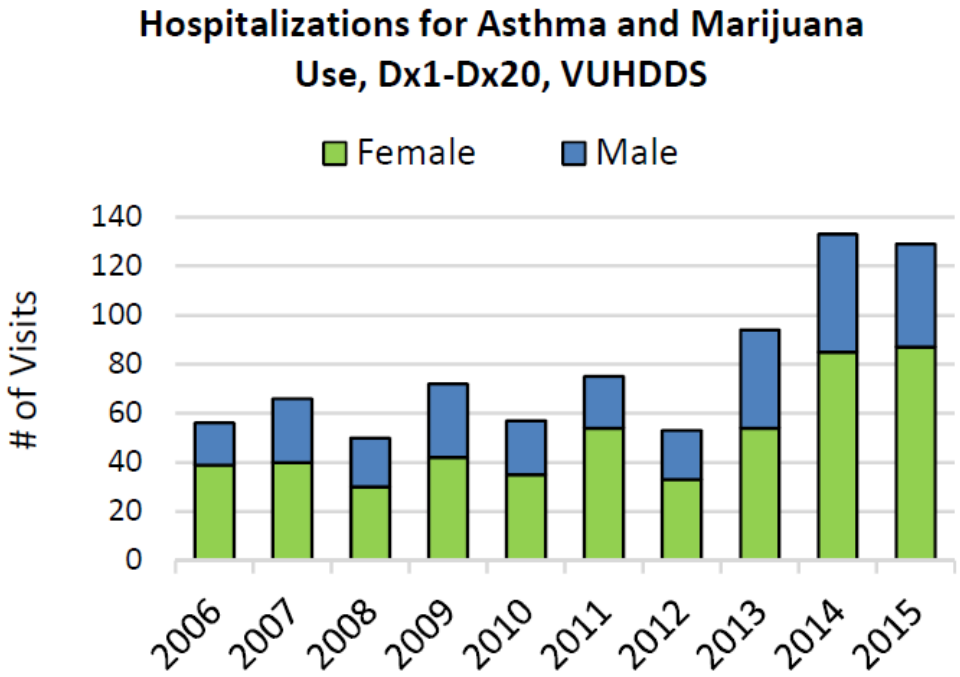
Vermont marijuana-related hospital admissions

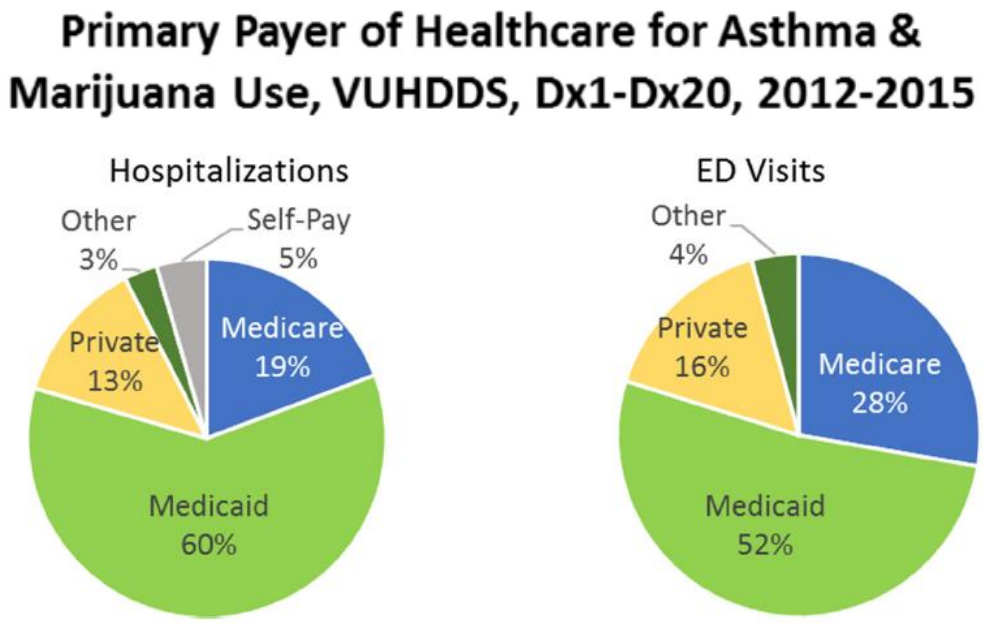


ED visits for marijuana-related asthma diagnosis in VT



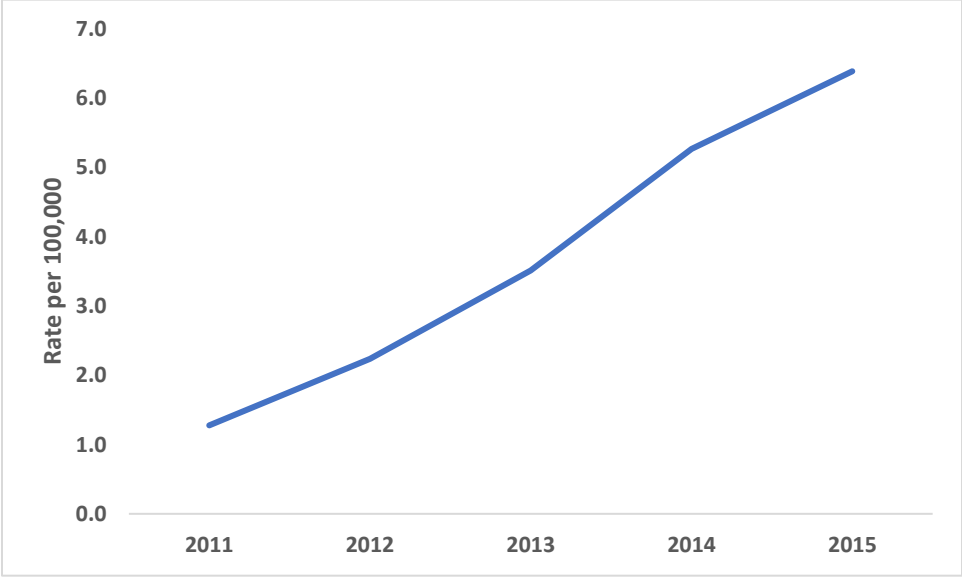
Hospitalizations for marijuana-related asthma diagnosis in VT



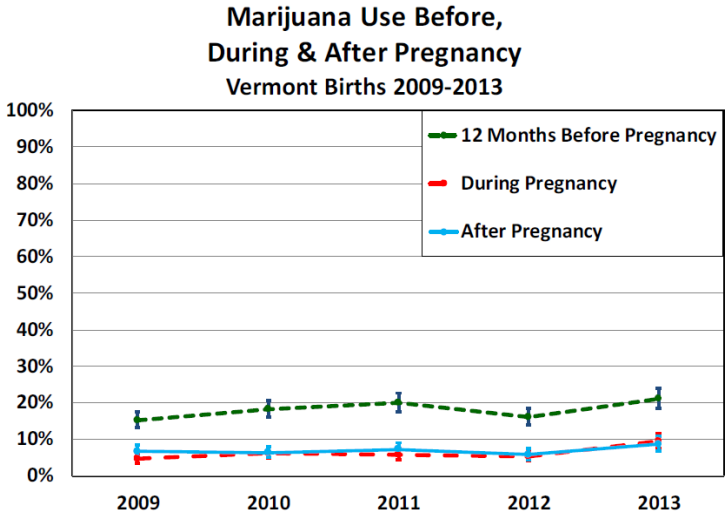


Cannabis Hyperemesis Syndrome

Below is a chart showing the change in the rate per 100,000 of individuals presenting to VT Emergency Departments with an injury code of R11.10 (vomiting, unspecified), 536.2 (persistent vomiting), or 787.03 (vomiting alone) who also had any cannabis-related diagnosis.

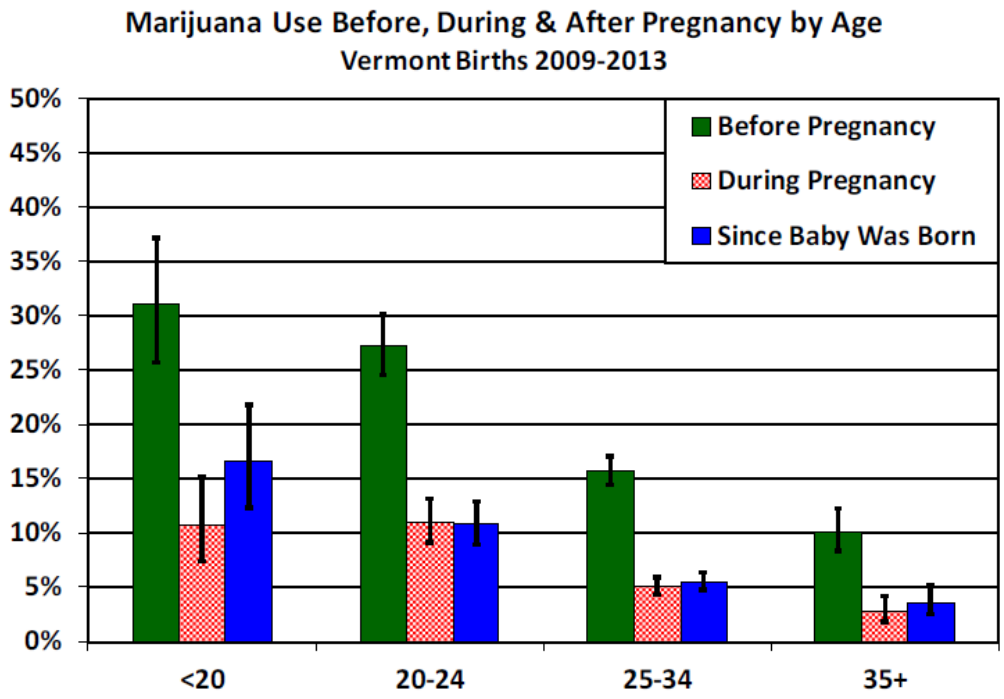


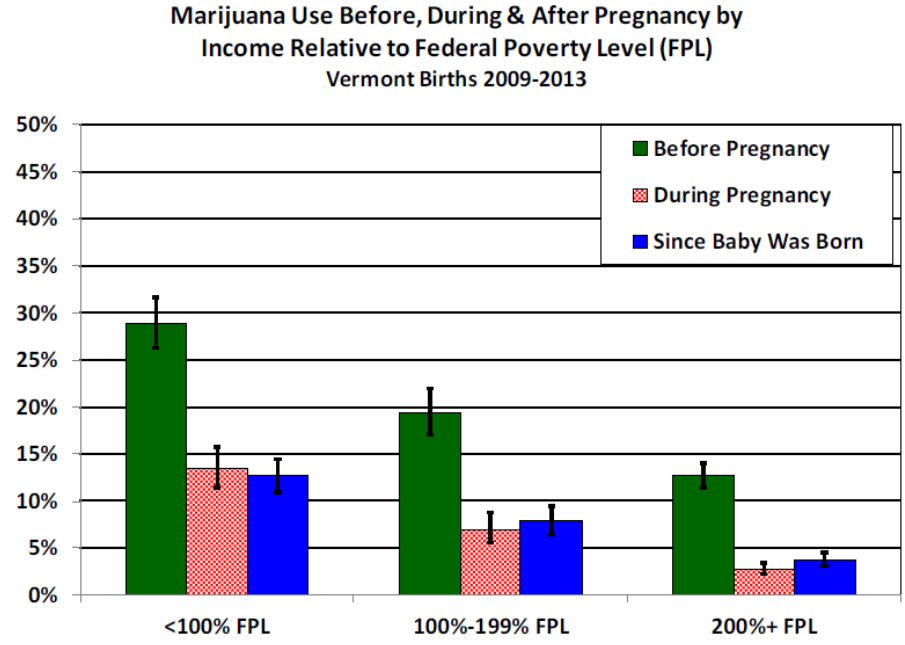
(i) Prenatal, perinatal exposure to marijuana[59]

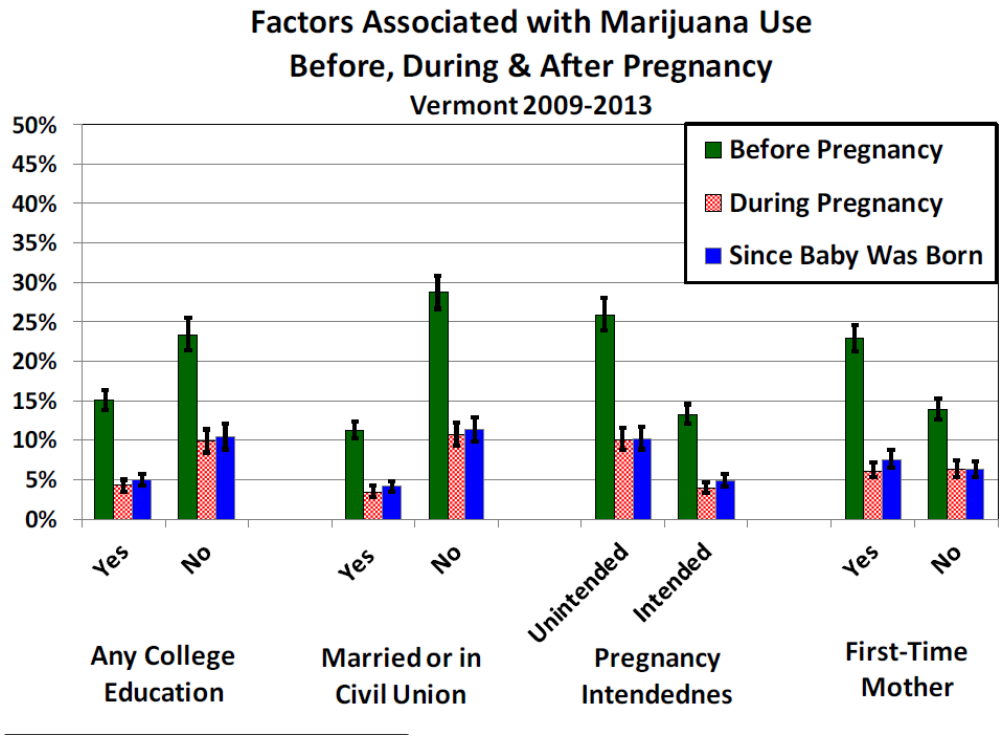


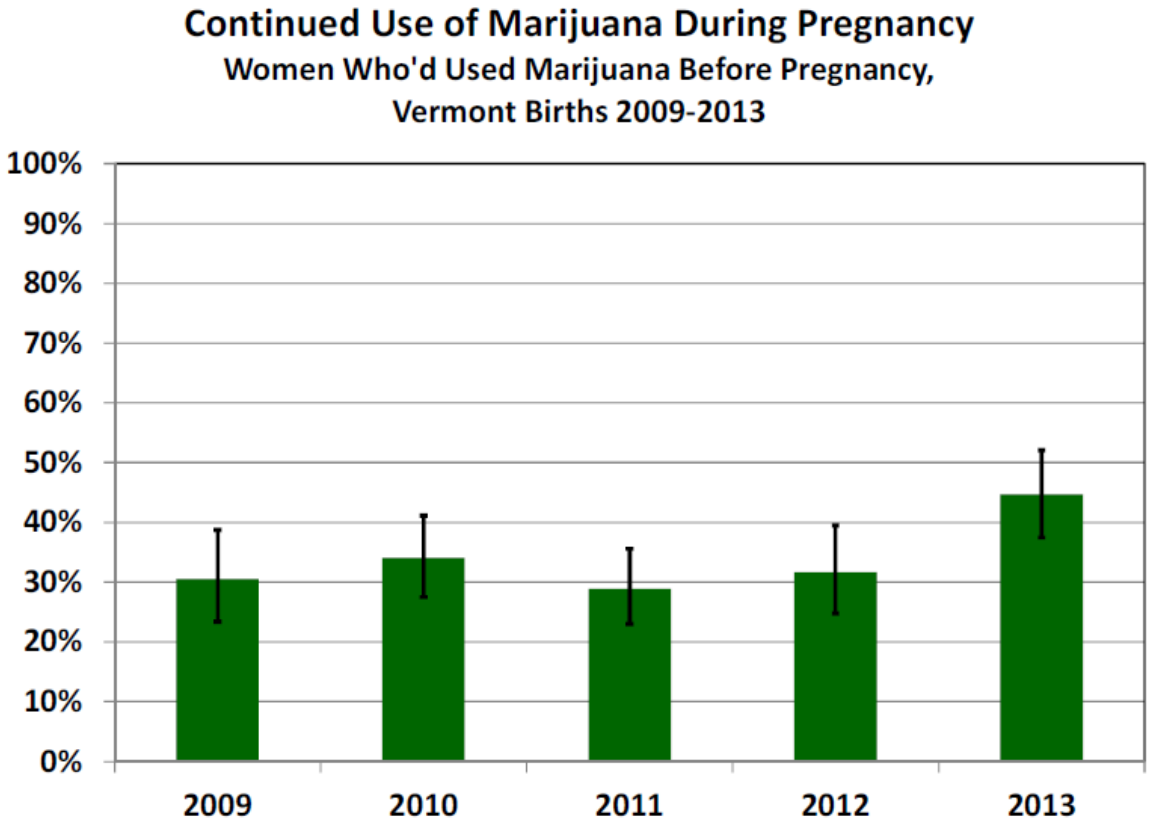
For Vermont births in the years 2009-2013, younger women and women in households with lower incomes were significantly more likely to smoke marijuana before, during and after pregnancy. In addition, marijuana use before, during, and after pregnancy is associated with lower educational attainment

[59] Data from Vermont Pregnancy Risk Assessment Monitoring system (PRAMS). http://www.healthvermont.gov/sites/default/files/documents/2017/02/PRAMS_Marijuana_2009_2013_corrected.pdf and http://www.healthvermont.gov/sites/default/files/documents/pdf/PRAMS%202014%20Births%20overview.pdf


Marijuana Use Before, During & After Pregnancy by Age
Vermont Births 2009-2013
50%
45%
40%
35%
30%
25%
20%
15%
10%
5%
0%
Before Pregnancy
During Pregnancy
Since Baby Was Born
<20
20-24
25-34
35+


Marijuana Use Before, During & After Pregnancy by
Income Relative to Federal Poverty Level (FPL)
Vermont Births 2009-2013
50%
45%
40%
35%
30%
25%
20%
15%
10%
5%
0%
Before Pregnancy
During Pregnancy
Since Baby Was Born
<100% FPL
100%-199% FPL
200%+ FPL


Factors Associated with Marijuana Use
Before, During & After Pregnancy
Vermont 2009-2013
50%
45%
40%
35%
30%
25%
20%
15%
10%
5%
0%
Before Pregnancy
During Pregnancy
Since Baby Was Born
Yes
No
Yes
No
Unintended
Intended
Yes
No
Any College Education
Married or in Civil Union
Pregnancy Intendednes
First-Time Mother


Continued Use of Marijuana During Pregnancy
Women Who'd Used Marijuana Before Pregnancy,
Vermont Births 2009-2013
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
2009
2010
2011
2012
2013

In 2014, 16% of pregnant women used marijuana in the year prior to pregnancy and 6% used marijuana during their pregnancy.

(iii) Psychosocial:

No Vermont data available.

(iv) Mental Health:

No Vermont data available.

(v) Problem Marijuana Use and
(vi) Marijuana Use and Abuse of Other Substances

Vermont data are extracted from the Substance Abuse Treatment Information System (SATIS). Individuals in treatment are assessed for primary, secondary, and tertiary substances of abuse.

Marijuana Treatment Admissions FY2010 – FY2017

FiscalYear	PeoplePrimary	PeopleSecondary	PeopleTeritary	AnyMJ
2010	1529	2148	677	4352
2011	1500	2235	690	4421
2012	1421	2364	833	4615
2013	1374	2359	1052	4783
2014	1374	2421	1221	5012
2015	1327	2414	1262	5000
2016	1202	2248	1340	4782
2017	1094	1987	1318	4384

When marijuana is a secondary or tertiary substance of abuse, there has been an increasing level of opioids as a primary substance of abuse:

Primary Substance when secondary is Marijuana (note: People can have multiple admits)

SubsCategory	2010	2011	2012	2013	2014	2015	2016	2017
Alcohol	1369	1355	1321	1253	1137	1128	971	861
Depressants	9	10	13	11	13	10	8	11
Hallucinogens	2	7	1	2	8	7	8	19
Opioids	672	749	942	1038	1221	1205	1209	1049
Other/Unknown	10	18	8	10	12	9	8	7
Stimulants	104	125	102	75	84	90	68	68

Primary Substance when tertiary is Marijuana (note: People can have multiple admits)

SubsCategory	2010	2011	2012	2013	2014	2015	2016	2017
Alcohol	151	130	141	154	140	120	125	106
Depressants	5	7	15	8	12	11	8	12
Hallucinogens	4	6	4	8	3	4	3	7
Opioids	439	481	623	830	1018	1085	1152	1145
Other/Unknown	1	11	6		4	4	2	5
Stimulants	85	74	62	70	67	61	73	74

Appendix 2
Weight-of-Evidence Categories[60]

CONCLUSIVE EVIDENCE
For therapeutic effects: There is strong evidence from randomized controlled trials to support the conclusion that cannabis or cannabinoids are an effective or ineffective treatment for the health endpoint of interest.

For other health effects: There is strong evidence from randomized controlled trials to support or refute a statistical association between cannabis or cannabinoid use and the health endpoint of interest.

For this level of evidence, there are many supportive findings from good-quality studies with no credible opposing findings. A firm conclusion can be made, and the limitations to the evidence, including chance, bias, and confounding factors, can be ruled out with reasonable confidence.

SUBSTANTIAL EVIDENCE
For therapeutic effects: There is strong evidence to support the conclusion that cannabis or cannabinoids are an effective or ineffective treatment for the health endpoint of interest.

For other health effects: There is strong evidence to support or refute a statistical association between cannabis or cannabinoid use and the health endpoint of interest.

For this level of evidence, there are several supportive findings from good-quality studies with very few or no credible opposing findings. A firm conclusion can be made, but minor limitations, including chance, bias, and confounding factors, cannot be ruled out with reasonable confidence.

MODERATE EVIDENCE
For therapeutic effects: There is some evidence to support the conclusion that cannabis or cannabinoids are an effective or ineffective treatment for the health endpoint of interest.

For other health effects: There is some evidence to support or refute a statistical association between cannabis or cannabinoid use and the health endpoint of interest.
For this level of evidence, there are several supportive findings from good- to fair-quality studies with

[60] From National Academies of Sciences, Engineering, and Medicine. 2017. *The health effects of cannabis and cannabinoids: The current state of evidence and recommendations for research.* Washington, DC: The National Academies Press. doi: 10.17226/24625.

very few or no credible opposing findings. A general conclusion can be made, but limitations, including chance, bias, and confounding factors, cannot be ruled out with reasonable confidence.

LIMITED EVIDENCE
For therapeutic effects: There is weak evidence to support the conclusion that cannabis or cannabinoids are an effective or ineffective treatment for the health endpoint of interest.

For other health effects: There is weak evidence to support or refute a statistical association between cannabis or cannabinoid use and the health endpoint of interest.

For this level of evidence, there are supportive findings from fair-quality studies or mixed findings with most favoring one conclusion. A conclusion can be made, but there is significant uncertainty due to chance, bias, and confounding factors.

NO OR INSUFFICIENT EVIDENCE TO SUPPORT THE ASSOCIATION
For therapeutic effects: There is no or insufficient evidence to support the conclusion that cannabis or cannabinoids are an effective or ineffective treatment for the health endpoint of interest.

For other health effects: There is no or insufficient evidence to support or refute a statistical association between cannabis or cannabinoid use and the health endpoint of interest.

For this level of evidence, there are mixed findings, a single poor study, or health endpoint has not been studied at all. No conclusion can be made because of substantial uncertainty due to chance, bias, and confounding factors.